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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,585	08/24/2006	Hirobumi Takahashi	BY0038P	8499

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,585	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30A, 30B-48* is/are pending in the application.

4a) Of the above claim(s) *48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30A, 30B-44, 47* is/are rejected.

7)☒ Claim(s) *45 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/16/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/JP05/04264 filed 03/04/2005 and claims priority to JAPAN 2004-062405 filed 03/05/2004.

Claims 30A, 30B-48 are pending. It is noted that claim 30 has been duplicated. New claims should be numbered consecutively in ascending order. 37 CFR 1.121 should be fully complied with in future claim amendments. The first claim 30 is now designated as 30A the second claim 30 is designated as claim 30B.

Response to Election/Restrictions

2. Applicant's election with traverse of Group II and the species, compound 33, in the reply filed on December 17, 2009 is acknowledged. The traversal is on the ground(s) that a special technical feature of a core structure is present. This is not found persuasive because the examiner had shown previously in the restriction requirement that such a structure was not novel. According to the applicant's representative claims 30A, 30B, 31, 33, 34, 36, 38, 39, 41-43, 45-46 read on the elected species. Claim 48 is withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Group II, Claims 30A, 30B, 31-47 drawn to compounds and compositions having a cyclohexa[c]pyridine core where X is carbon and n is 0. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 30B-44, 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 47 depends from claim 20, a canceled claim. Claims 30B-44 depend on claim 29 a canceled claim. These dependent claims 30B-44, 47 have been examined as a courtesy as though they depend from claim 30A, even though they could be properly rejected under 112 2nd only. A claim amendment correcting all claim numbering and dependency issues is expected in the next communication.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 30A, 30B-44, 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where only one of A1-A4 is N, and only one of A5-A8 is N, R6 is defined as in claim 33, R1 and R1' as in claims 34-35, R7 is as described in claim 40-41, R2 and R2' are as in claims 36 and 37 and R3 and R3' are as described in claim 38 and R4 is as described in claims 39-40 and their appropriate generic descriptions (i.e. fluorine supports halogen, methyl supports alkyl and so on), it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with

these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a huge list of propehtic rings, and other groups bearing multiple further substitutions.

(B) The nature of the invention: This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as opioid receptor like 1 (ORL-1) ligands.

(D) The level of one of ordinary skill: One of ordinary skill is an organic/medicinal chemist.

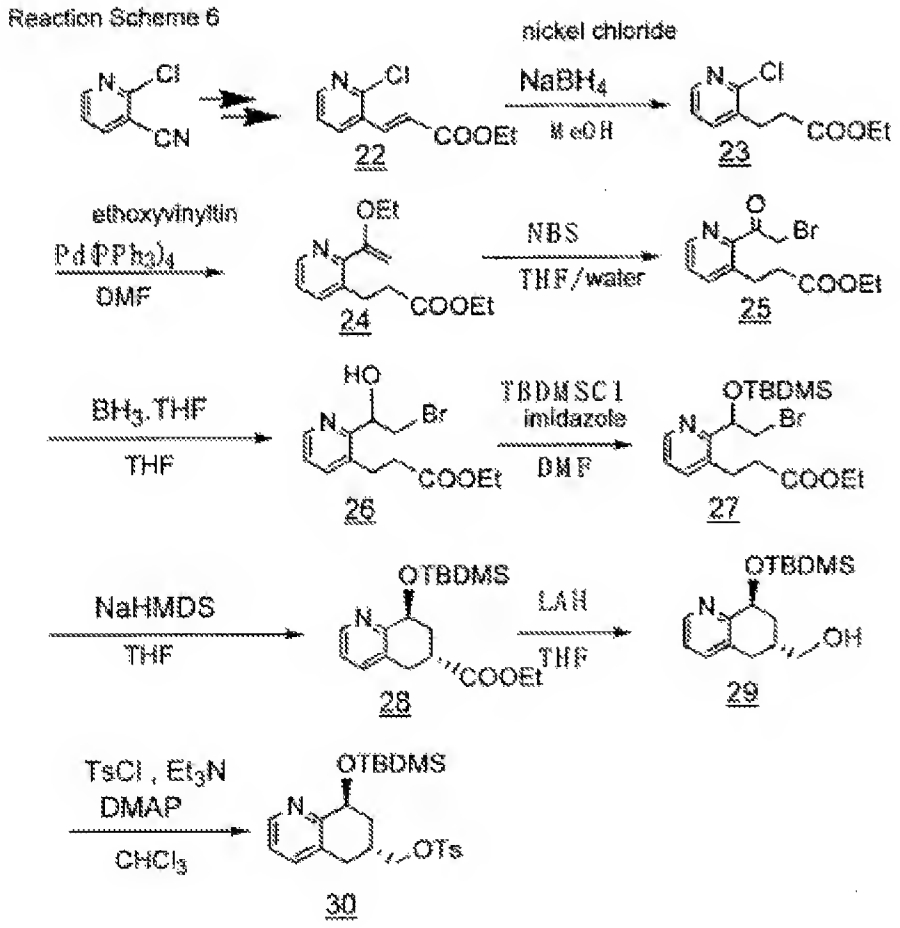
(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

The limitations inherent to the paucity of available starting materials are readily apparent, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after

extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. **The same can be said if certain chemicals are required to make a compound or practice a chemical process.** In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The applicant has provided us with a synthesis for the X-Y quadruple A containing ring. Shown below:



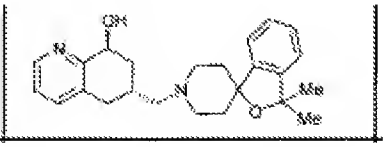
It is very clear that no starting materials are described or made available for synthesis of rings other than quinoline. Indeed in order to be enabled for all the various rings a vast array of new syntheses would need to be developed. There is no such synthetic methodology currently available. The instant claims are drawn to teratzines i.e. where all A's are N. These compounds are not isolable and useable unless conjugated to an aromatic ring. Here the ring is saturated. See Churakov et. al. "Progress in 1,2,3,4-Tetrazine" Chemistry Chemical Reviews 2004, 104, 2601-2616. On pg. 2609 ff. the stability and syntheses of these compounds are discussed. The synthesis of variably substituted heterocycles and other aromatics represents a vast area of basic chemical research and the development of new methodology in order to reach these materials is a serious undertaking, and the current state of the art does not allow the practicing chemist to prepare the compounds of the claimed scope. According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring materials are to be obtained. Where may the directions to prepare or buy them be found? See *In re Howarth*, 210 USPQ 689, (claimed

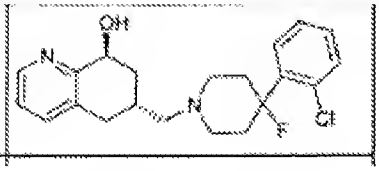
derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

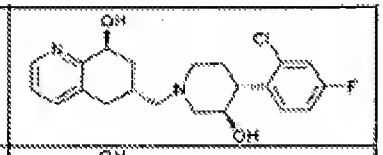
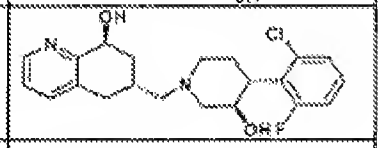
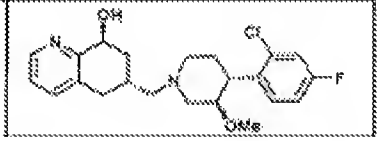
While some modest group of compounds outside those exemplified might be prepared by a skilled artisan, the paucity of working examples point to the key deficit in the disclosure, namely that the "how to use" requirement of 112 1st paragraph has not been met. While organic chemistry is highly unpredictable, the degree of unpredictability in the pharmaceutical art is even greater. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

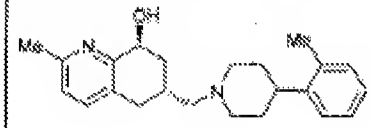
> "….. compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure…(pg. 4536 column 2, line 9)…..This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions) **(H).**

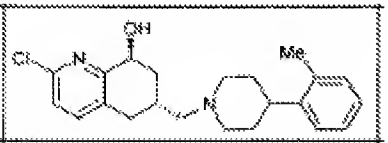
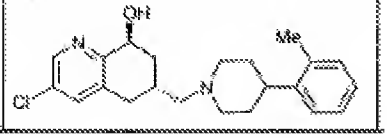
The instant claims are drawn to an enormously broad recitation of prophetic moieties. The only example examples that read on the elected invention are shown below:

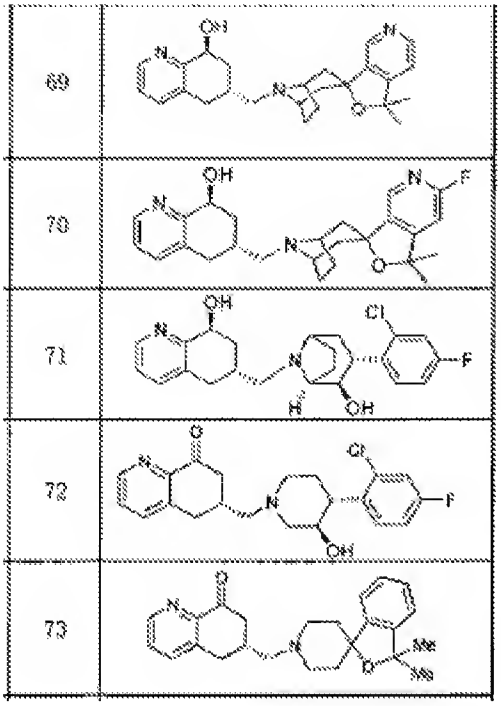
25	

29	

33	
34	
35	

No.	Structural Formula
66	

63	
64	



It is clear that in terms of substituents these are only very small simple groups. The examiner submits that structural requirements for binding to the ORL-1 receptor are stringent, and that the working examples shown above do not lead to the broad genus description. The following publication is submitted as evidence:

Sugimoto et. al. "Design, synthesis, and biological evaluation of indole derivatives as novel nociceptin/orphanin FQ (N/OFQ) receptor antagonists" Bioorganic & Medicinal Chemistry Letters 16 (2006) 3569–3573.

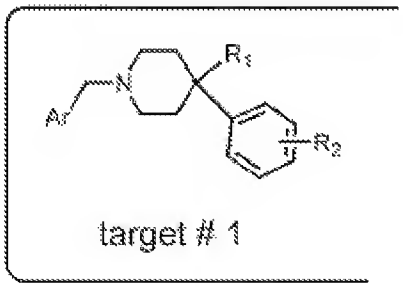
This journal article describes the state of the art in ORL-1 receptor drug development, an excerpt is shown below:

"Our initial efforts toward understanding the SAR of the lead molecule were focused on replacing the substituted phenylethyl group with other substituents and heteroaromatic nuclei. The results of this study are summarized in Table 1. Compounds 31–43 were prepared to evaluate the effects of the linker length and substituents. Optimal binding for ORL1 was achieved with our lead compound 33. A shorter linker (32) or longer spacer (34) **resulted in poor or loss of affinity for ORL1.** Attempts to introduce heteroatom (43) on the linker leading the ether linkage also **resulted in inactive compound.** Removing the substituent from the phenyl

group to give **the unsubstituted derivative 31 or replacing the phenyl group with pyridine, as in examples 40–42, led to complete loss of activity.** In addition, replacement of the substituent on the phenyl ring with other functional groups, 4-fluoro (35), 4- methyl (36), and 4-methoxy (37), gave compounds 2- to 6-fold less potent. However, 4-trifluoromethyl analog 39 was approximately 2-fold more potent than the 4-chloro compound 33.

The phenyl group was then replaced with alkyl or cycloalkyl moieties to confirm whether aromatic substituents are essential..... Attempts to introduce hydrophilic heteroatoms on the alkyl region leading ether or amino analogs (C log P 2.06–2.50) **resulted in inactive compounds** (54–56)." pg. 3571, ..."As shown in Table 3, the C-5, C-6, and C-7 substituted analogs 59–61, respectively, **were inactive** when compared with C-4 analog 33." pg. 3572

Clearly the property of ORL-1 binding is an unpredictable hit or miss affair. As further evidence and to give a more complete description of the art, the study of Chen et. al. "Design and Parallel Synthesis of Piperidine Libraries Targeting the Nociceptin (N/OFQ) Receptor." Bioorganic & Medicinal Chemistry Letters 2003, 13, 3247–3252 is illustrative. In this study, the authors took fragments from known piperidine based ORL-1 ligands and constructed a hypothetical pharmacophore (see Figure 1) and then proposed two target libraries to screen. Target 1 is remarkably similar to the core of the instant claims:



Ar is in the words of Figure 1 a "large hydrophobic group". Paradoxically, the addition of a single methyl group in the naphthyl compound AL9P6 resulted in a complete loss of activity, as compared to compound AL10P6 (see Table 3, page 3250). Even a very minor change of H to Me does not lead to predictable behavior.

These references serve to show that the structure of a compound actually determines its activity at the ORL-1 receptor and guessing which compound might have such activity is not possible. While some experimentation is possible, the references provided serve to show that the choice of substituents even with experimentation is generally limited to halogens, alkyl groups, nitriles, alkoxy, and other small moieties. In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). The long list of the prophetic groups includes very large groups, many basic and polar moieties and the evidence shows that these modifications would not lead to compounds that maintain utility. Making the full scope of the compounds is undue experimentation as shown above and evidenced by statements of a skilled artisan, Derek Lowe, a Ph.D. medicinal chemist who has worked for numerous drug companies and runs the website "In the Pipeline" describes claims like those of the instant case in the following way:

"I've seen many claims that couldn't be fully enabled short of putting five hundred people to work on them full-time for about ten years." (In the Pipeline, online, accessed June 16, 2008, "http://pipeline.corante.com/archives/2006/01/24/the_examiner_finally_snaps.php")

In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The

specification gives very little guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. While working examples are not required, in nascent technologies, such as the instant case, the degree of unpredictability is an important factor. See MPEP 2164.02 for guidance regarding the size of claimed genus. See *Ex parte WEIL AND SCHLICHTING*, 158 USPQ 620 (Bd. Pat. App. & Int. 1967)

"We will sustain this rejection of the claims as we are in accord with the examiner's position. We find no support in the disclosure for such compounds encompassed by these claims wherein R 1, R 2, R 3, and R 5are all the same and selected from the group, lower alkyl , hydroxy , alkoxy , di(loweralkyl)amino and nitro for example. These claims appear to be in the nature of a paper concept wherein all possible substituents have been included in the composition. There are no examples of such compounds which are included within the vast scope encompassed by these claims, although appellants have a considerable disclosure with respect to certain components but this does not warrant claims of the enormous breadth recited."

In addition see *In re Fouche* 169 USPQ 429 which dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

and *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976):

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See In re Ellis, 37 App. D. C. 203; In re Dosselman, 37 App. D. C. 211; In re Langmuir, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (affirmed):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the invention claimed shall be no broader than the invention set forth in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only certain aryl radicals and certain specifically substituted aryl radicals would be suitable for such purposes." This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case we have only a few working examples and clearly as shown by the discussion above the state of the art is highly unpredictable and undue experimentation would be required to practice the invention. A traversal of this rejection would suggest that changes such as replacing the phenyl group with pyridine, as described by Sugimoto, are in fact routine and predictable and that all "large hydrophobic group[s]" are art recognized equivalents.

Objections

5. Claims 45-46 are objected to for containing non-elected subject matter, but would be allowable if the non-elected material were removed.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JANET ANDRES can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David K. O'Dell/
Examiner, Art Unit 1625